

<p style="text-align: center;">Glycopyrronium Bromide 200 micrograms/ml Injection Summary of Product Characteristics</p>
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1. NAME OF THE MEDICINAL PRODUCT

Glycopyrronium Bromide 200 micrograms/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of sterile solution for injection contains 200 micrograms of glycopyrronium bromide.

Each 3 ml of sterile solution for injection contains 600 micrograms of glycopyrronium bromide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, sterile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. To protect against the peripheral muscarinic actions of anticholinesterases such as neostigmine and pyridostigmine, used to reverse residual neuromuscular blockade produced by non-depolarising muscle relaxants.
2. As a pre-operative antimuscarinic agent to reduce salivary, tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.
3. As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia with the use of suxamethonium or due to cardiac vagal reflexes.

4.2 Posology and method of administration

Route of Administration: Intravenous or intramuscular injection.

Dosage:

Premedication:

Adults and elderly patients:

200 - 400 micrograms or 4 - 5 micrograms/kg to a maximum of 400 micrograms intravenously or intramuscularly.

Children:

4 - 8 micrograms/kg to a maximum of 200 micrograms intramuscularly or preferably by intravenous injection.

Larger doses may result in a profound and prolonged antisialagogue effect which may be unpleasant for the patient.

Intra-operative use:

Adults and elderly patients:

By intravenous injection: A single dose of 200 - 400 micrograms or 4 - 5 micrograms/kg to a maximum of 400 micrograms, repeated if necessary.

Children:

By intravenous injection: A single dose of 200 micrograms by intravenous injection should be used. Alternatively, a single dose of 4 - 8 micrograms/kg up to a maximum of 200 micrograms may be used. This dose may be repeated if necessary.

Reversal of residual non-depolarising neuromuscular block:

Adults and older patients:

200 micrograms (0.2 mg) intravenously per 1000 micrograms (1 mg) neostigmine or the equivalent dose of pyridostigmine. Alternatively, a dose of 10 to 15 micrograms/kg (0.01 to 0.015 mg/kg) intravenously with 50 micrograms/kg (0.05 mg/kg) neostigmine or equivalent dose of pyridostigmine. Glycopyrronium bromide may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

Children:

10 micrograms/kg (0.01 mg/kg) intravenously with 50 micrograms/kg (0.05 mg/kg) neostigmine or the equivalent dose of pyridostigmine. Glycopyrronium bromide may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

4.3 Contraindications

In common with other antimuscarinics: angle-closure glaucoma; myasthenia gravis (large doses of quaternary ammonium compounds have been shown to block end plate nicotinic receptors); paralytic ileus; pyloric stenosis; prostatic enlargement.

Anticholinesterase-antimuscarinic combinations such as neostigmine plus glycopyrronium should be avoided in patients with a prolonged QT interval.

4.4 Special warnings and precautions for use

Antimuscarinics should be used with caution (due to increased risk of side effects) in Down's Syndrome, in children and in the elderly.

They should also be used with caution in gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, acute myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) because of the increase in heart rate produced by their administration, coronary artery disease and cardiac arrhythmias, pyrexia (due to inhibition of sweating), pregnancy and breast feeding.

Because of prolongation of renal elimination, repeated or large doses of glycopyrronium bromide should be avoided in patients with uraemia.

Large doses of quaternary anticholinergic compounds have been shown to block end plate nicotinic receptors. This should be considered before using glycopyrrolate in patients with myasthenia gravis.

It is known that the administration of anticholinergic agents during inhalation anaesthesia can result in ventricular arrhythmias.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e essentially sodium- free.

4.5 Interaction with other medicinal products and other forms of interaction

Many drugs have antimuscarinic effects; concomitant use of two or more of such drugs can increase side-effects such as dry mouth, urine retention and constipation. Concomitant use can also lead to confusion in the elderly.

Anticholinergic agents may delay absorption of other medication given concomitantly.

Concurrent administration of anticholinergics and corticosteroids may result in increased intraocular pressure.

Concurrent use of anticholinergic agents with slow-dissolving tablets of digoxin may cause increased serum digoxin levels.

Ritodrine: tachycardia

Increased antimuscarinic side-effects: amantadine; tricyclic antidepressants; antihistamines; clozapine; disopyramide; MAOIs; nefopam; pethidine; phenothiazines (increased antimuscarinic side effects of phenothiazines but reduced plasma concentrations)

Possibly increased antimuscarinic side-effects: tricyclic (related) antidepressants

Domperidone/Metoclopramide: antagonism of effect on gastrointestinal activity

Ketoconazole: reduced absorption of ketoconazole

Levodopa: absorption of levodopa possibly reduced

Memantine: effects possibly enhanced by memantine

Nitrates: possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)

Parasympathomimetics: antagonism of effect

4.6 Pregnancy and lactation

Data on the use of glycopyrronium bromide in pregnant women, other than on delivery, are not forthcoming, nor is there documentation concerning excretion in breast milk.

Although reproduction studies in rats and rabbits at up to 1000 times the human dose revealed no teratogenic effects from glycopyrronium bromide, safety in human pregnancy has not been established.

Diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner.

Studies in dogs suggest that the former may be due to diminished seminal secretion which is evident at high doses of glycopyrronium bromide. The significance of these findings for man is not clear. Although glycopyrronium bromide does not readily cross the placenta, the injection should only be prescribed to pregnant women when clearly necessary.

Caution is advised when considering administration to a nursing mother.

4.7 Effects on ability to drive and use machines

Glycopyrronium Bromide 200 micrograms/ml Injection is used in anaesthesia. It is not anticipated that patients will be driving or operating machinery under its influence. However, systemic administration of antimuscarinics may cause blurred vision, dizziness and other effects that may impair a patient's ability to perform skilled tasks such as driving. These activities should not be undertaken until any disturbance of visual accommodation or balance has resolved.

4.8 Undesirable effects

Side effects of antimuscarinics such as glycopyrronium bromide are basically extensions of the fundamental pharmacological action. These include constipation, transient bradycardia (followed by tachycardia, palpitations and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin.

Side effects that occur occasionally include confusion (particularly in the elderly), nausea, vomiting and giddiness.

4.9 Overdose

Glycopyrronium bromide is a quaternary ammonium agent and symptoms of overdosage are peripheral rather than central in nature. Excessive peripheral anticholinergic effects may be countermanded by giving intravenously a quaternary ammonium anticholinesterase such as neostigmine methylsulphate in increments of 0.25mg in adults. The dose may be repeated every 5 – 10 minutes until anticholinergic over-activity is reversed or up to a maximum of 2.5mg. Proportionately smaller doses should be used in children.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glycopyrronium bromide (ATC Code: A03AB02) is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine. It is used similarly to atropine in anaesthetic practice. Given as a premedicant before general anaesthesia, it diminishes the risk of vagal inhibition of the heart and reduces salivary and bronchial secretions. Intra-operatively, it may be given to reduce bradycardia and hypotension induced by drugs such as suxamethonium, halothane or propofol. Glycopyrronium bromide may be used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects.

Antimuscarinic drugs are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves, as well as being inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation.

Peripheral antimuscarinic effects that are produced as the dose increases are: decreased production of secretions from the salivary, bronchial and sweat glands; dilatation of the pupils (mydriasis) and paralysis of accommodation (cyclopegia); increased heart rate; inhibition of micturition and reduction in gastrointestinal tone; inhibition of gastric acid secretion.

Quaternary ammonium compounds are sparingly lipid soluble and do not readily pass lipid membranes such as the blood-brain barrier. Central effects are negligible.

5.2 Pharmacokinetic properties

Following intravenous administration, onset of action occurs within one minute, with peak activity at around 5 minutes.

Following intramuscular injection, maximum plasma concentration and onset of action of glycopyrronium bromide is achieved within 30 minutes. Peak effects occur after approximately 30 - 45 minutes; vagal blocking effects last for 2 – 3 hours and antisialagogue effects persist for 7 - 8 hours. There is a faster absorption rate when glycopyrronium bromide is injected into the deltoid muscle rather than into the gluteal or vastus lateralis muscles. Although the elimination half life of glycopyrronium bromide from plasma is within 75 minutes, quantifiable levels may remain up to 8 hours after administration.

Cerebrospinal fluid levels of glycopyrronium bromide remain below detection level up to one hour after therapeutic dosing.

Following either intravenous or intramuscular administration, 50% of glycopyrronium bromide is excreted in the urine in 3 hours in non-uraemic individuals; renal elimination is considerably prolonged in patients with uraemia. Appreciable amounts are excreted in bile. In 48 hours, 85% has been excreted into the urine. About 80% of the excreted amount is as unchanged glycopyrronium bromide or active metabolites.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid, concentrated
Sodium chloride
Water for injections

6.2 Incompatibilities

Glycopyrronium Bromide 200 micrograms/ml Injection has been shown to be physically compatible with the following agents commonly used in anaesthetic practice: Butorphanol, Lorazepam, Droperidol, and Fentanyl Citrate, Levorphanol Tartrate, Pethidine Hydrochloride, Morphine Sulphate, Neostigmine, Promethazine and Pyridostigmine.

Glycopyrronium Bromide 200 micrograms/ml Injection has been shown to be physically incompatible with the following agents commonly used in anaesthetic practice: Diazepam, Dimenhydrinate, Methohexitone Sodium, Pentazocine, Pentobarbital Sodium and Thiopental Sodium.

6.3 Shelf Life

1 ml ampoule- 24 months
3 ml ampoule- 18 months

6.4 Special precautions for storage

Do not store above 25°C.
Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type 1 glass ampoules, 1 ml and 3 ml.
Pack sizes: 10 x 1 ml ampoules, 10 x 3 ml ampoules.

6.6 Special precautions for disposal

For single use only.
Any unused solution should be discarded immediately after initial use.
The injection should not be used if particles are present.

7. MARKETING AUTHORISATION HOLDER

Taro Pharmaceuticals Ireland Limited,
Lourdes Road,
Roscrea,
Co. Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

PL 20910/0003

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF
AUTHORISATION**

01/04/2008

10. DATE OF REVISION OF THE TEXT

01/04/2008

Legal Status

POM